Ozone-mediated Reaction of Anilides and Phenyl Esters with Nitrogen Dioxide: Enhanced *Ortho*-reactivity and Mechanistic Implications

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In the presence of ozone, anilides **1** can be nitrated rapidly with nitrogen dioxide in chloroform at 0 °C to give a high proportion of *ortho*-nitro derivatives (*ortho*:*para* = 1.2–4.4) in good yields. The phenyl esters **15** can be similarly nitrated on the aromatic ring without significant cleavage of the ester bond, giving a mixture of isomeric nitro derivatives in which the *ortho*-isomer predominates (*ortho*:*para* = 1.1–1.5). The origin of the enhanced *ortho* reactivity is discussed in terms of an electron-transfer process involving the nitrogen trioxide as initial electrophile.

The nitration of aromatic compounds is usually carried out under acidic conditions using nitric acid as a source of the nitro group. We have recently reported an alternative methodology for aromatic nitration, in which nitrogen dioxide acts as a good nitrating agent for aromatic systems in the presence of ozone (kyodai-nitration).[1,2] The direct use of nitrogen dioxide as a source of the nitro group has considerable potential in the chemical industry in that it dispenses both with the energy-consuming multistep process for manufacturing concentrated nitric acid from the lower oxides of nitrogen and the disposal of spent acids. The kyodai-nitration can be carried out under non-acidic conditions, the products of which are often characterized by a unique distribution of the isomeric products.[3] As part of our continuing effort to define the scope and elucidate the mechanism of this novel nitration, we now describe the ozone-mediated reaction of the anilides **1** and the phenyl esters **15** with nitrogen dioxide. The acylamino group in compound **1** and acyloxy group in compound **15** are both conjugatively electron-releasing and inductively electron-withdrawing, the former effect being, as a whole, of greater consequence than the latter.

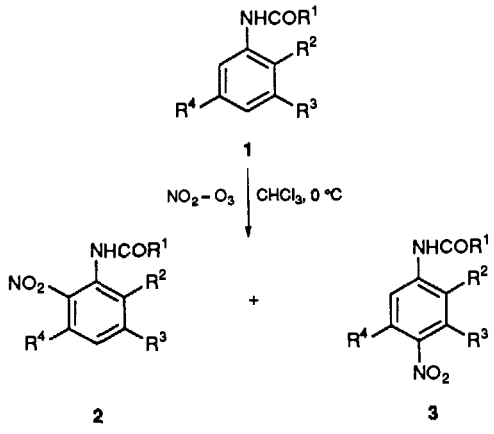
Results and Discussion

Kyodai-nitration of Anilides **1**.—Aromatic 1,2-diamines, important synthetic intermediates for a variety of pharmaceuticals, agricultural drugs and dyestuffs, are usually prepared by the reduction of 1,2-nitro amines which, in turn, are obtained from the nitration of acetanilides followed by hydrolysis or from the ammonolysis of 1,2-chloronitroarenes. The latter route lacks generality and is highly dependent on the availability of starting materials.

When the acetanilides **1a–f** were subjected to the kyodai-nitration, we were surprised to observe a high proportion of *ortho*-substitution (Scheme 1, Table 1). The *ortho*:*para* ratios of nitroacetanilides obtained were comparable with those found in the classical nitration with nitric acid–acetic anhydride.[4,5] The reaction was clean and no resinous substances were formed.

Dichloromethane and chloroform were the solvents of choice. The reaction occurred more quickly in the former solvent, while the degree of the positional selectivity was higher in the latter solvent (Table 2). In carbon tetrachloride and tetrachloroethylene, the *ortho*-selectivity decreased. No *meta*-substitution was observed. When ozonized oxygen was replaced by ozonized air, the reaction became slower and the *ortho*:*para* ratio of the products decreased. In the absence of ozone, the reaction was quite sluggish and the nitro group entered almost exclusively into the *para* position when the conversion was low. Prolonged contact led to a complex mixture of products.

The hydrogen atom of the amide group in compound **1**



a R^1 = Me, R^2 = R^3 = R^4 = H
b R^1 = R^2 = Me, R^3 = R^4 = H
c R^1 = R^3 = Me, R^2 = R^4 = H
d R^1 = R^2 = R^3 = Me, R^4 = H
e R^1 = R^2 = R^4 = Me, R^3 = H
f R^1 = R^3 = R^4 = Me, R^2 = H
g R^1 = Me, R^2 = MeO, R^3 = R^4 = H
h R^1 = Me, R^2 = R^4 = H, R^3 = MeO
i R^1 = Me, R^2 = R^4 = H, R^3 = Cl
j R^1 = Me, R^2 = NO_2, R^3 = R^4 = H
k R^1 = Me, R^2 = R^4 = H, R^3 = NO_2
l R^1 = Et, R^2 = R^3 = R^4 = H
m R^1 = Pr^i, R^2 = R^3 = R^4 = H
n R^1 = Bu^t, R^2 = R^3 = R^4 = H
o R^1 = Ph, R^2 = R^3 = R^4 = H
p R^1 = CH_2Cl, R^2 = R^3 = R^4 = H
q R^1 = $CHCl_2$, R^2 = R^3 = R^4 = H
r R^1 = CCl_3, R^2 = R^3 = R^4 = H
s R^1 = CF_3, R^2 = R^3 = R^4 = H

Scheme 1

appears to play an important role in determining the proportion of the *ortho* isomer. Thus, when *N*-methylacetanilide **4** was subjected to ordinary nitration, it underwent complete *para*-substitution in both mixed acid and nitric acid–acetic anhydride systems.[6] In the kyodai-nitration, however, a high *ortho*-selectivity (*ortho*:*para* = 3.3) was achieved irrespective of the absence of the amide hydrogen atom in compound **4** (Scheme 2). The enhanced *ortho*-reactivity disappeared when the nitro group was located at a position *ortho* to the amide function; further nitration of 2-nitroacetanilide **1j** by the present procedure led to the 2,4-dinitro compound **3j** rather than the 2,6-dinitro isomer **2j** (2,4:2,6 ratio = 2.2–2.5). Such a decrease in *ortho*-reactivity may be attributed either to a special interaction between the amide hydrogen atom and the nitro group in a close proximity,[6] or a change-over of the reaction mechanism as discussed below. Nitroacetanilides are unaffected by nitric acid–acetic anhydride at 0 °C,[6] but they underwent smooth nitration under our low temperature conditions.

Table 1 Kyodai-nitration of the acetanilides **1**[a]

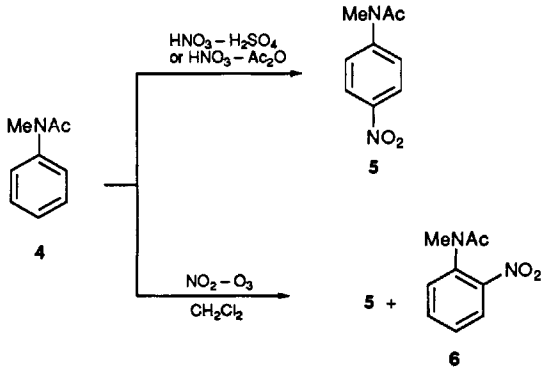
Substrate	Reaction time (h)	Yield (%)	*o*:*p* Ratio[b]
1a	2.5	99	4.4 (0.05, 4.5)[c] (0.04, 3.3)[d]
1b	2.0	93	1.6
1c	2.0	99	3.2[e]
1d	1.5	81	4.4 (—, 4.5)[c]
1e	1.5	96	2.8
1f	1.5	78	2.2
1g[f]	1.0	99	0[g]
1h[f]	1.0	99	1.9 (0.05, 4.0)[c]
1i	3.0	96	3.5[h]
1j	3.0	95	0.45
1k	3.0	98	2.8[i]
1l	2.5	87	1.4
1m	1.5	91	2.3
1n	0.2	Complex mixture	—
1o	2.0	97	2.2
1p	3.0	88	2.3 (0.15, 4.0)[d]
1q	2.5	72	2.4
1r	3.5	99	1.5
1s	4.5	97	1.2 (0.25, 0.51)[d]

[a] All reactions were carried out using the given substrate (10 mmol) in chloroform (50 cm^3) at 0 °C. [b] Product compositions were determined by GLC. [c] From ref. 5. The numbers in parentheses refer to the values obtained by HNO_3–H_2SO_4 and by HNO_3–$(MeCO)_2O$ systems, respectively. [d] From ref. 6. See footnote *c*. [e] Mononitration product was composed of 2-nitro (21%), 4-nitro (24%) and 6-nitro (55%) isomers. [f] Air was used as an ozone source. [g] Mononitration product was composed of 4-nitro (91%) and 5-nitro (9%) isomers. [h] Mononitration product was composed of 2-nitro (17%), 4-nitro (2%) and 6-nitro (61%) isomers. [i] Mononitration product was composed of 3,4-dinitro (12%), 3,5-dinitro (54%) and 2,5-dinitro (34%) isomers.

Table 2 Effect of solvents on *o*:*p* isomer ratios in the kyodai-nitration of acetanilide **1a**

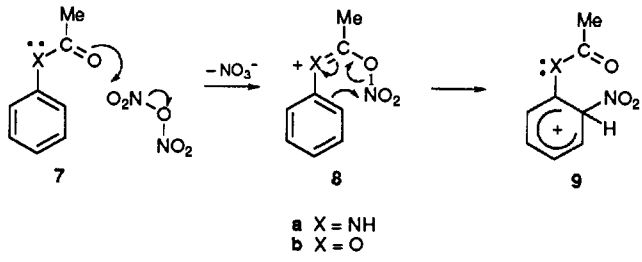
Solvent	Reaction time (h)	Yield (%)	*o*:*p* Ratio
CH_2Cl_2	2.5	98	3.6
$CHCl_3$	2.5	99	4.4
CCl_4	2.0	98	1.8
CCl_2=CCl_2	1.5	93	2.0
$CHCl_3$[a]	6.0	97	2.2
$CHCl_3$[b]	2.5	98	4.5

[a] Air was used as an ozone source. [b] 4-Dimethylaminopyridine (20 mol%) was added.

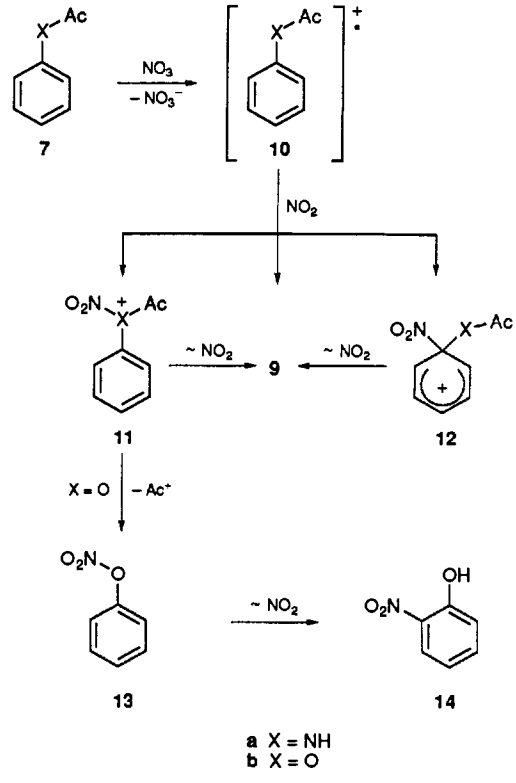


Scheme 2

The nitration of acetanilide **1a** has a history of controversy over the way in which the nitro group enters into the aromatic nucleus and the problem apparently remains unsettled.[4–6] The nitration with nitric acid in acetic anhydride gives *ortho*:*para* isomer ratios greater than unity (up to 9), whereas the nitration with mixed acid shows *ortho*:*para* ratios in the range of 0.01–0.8.



Scheme 3



Scheme 4

The former nitration has generally been accepted to proceed *via* a molecular process in which dinitrogen pentaoxide reacts in a polarized form. The latter nitration involves electrophilic attack of a nitronium ion on a neutral substrate or its conjugate acid depending on the acidity of the reaction medium. The kyodai-nitration of the anilides **1** may be expected to proceed *via* two different reaction pathways; one is electrophilic nitration with dinitrogen pentaoxide,[7] a process which has long been known to lead to a high proportion of *ortho*-substitution (Scheme 3). Another is electron-transfer nitration,[8] where nitrogen trioxide, generated *in situ* from nitrogen dioxide and ozone, oxidizes the anilide **7a** to a radical cation **10a**, which is captured by nitrogen dioxide to form preferential precursors **9a**, **11a** and **12a**, eventually leading to the *ortho*-nitro derivative (Scheme 4). On the basis of the theoretical considerations made in the next section, we favour the latter mechanistic pathway at present.

The present non-acid procedure for aromatic nitration is attractive for large-scale preparations of aromatic 1,2-nitro amines, since the classical procedure based on the nitric acid–acetic anhydride system needs careful control because of the exothermic nature of the reaction and the explosive nature of acetyl nitrate which is generated *in situ*.[9] An additional advantage is the use of recoverable solvents such as dichloromethane, chloroform, nitromethane, acetonitrile, *etc.*, in place of expensive acetic anhydride which is completely destroyed by aqueous work-up after the reaction.

Table 3 Kyodai-nitration of the aryl esters **15a–d**[a]

Substrate	Reaction time (h)	Conversion (%)	Yield (%)[b]	Isomer distributions (%)[c] *o*:*m*:*p*	*o*:*p* Ratio
15a	1	74	56	58: < 1: 41	1.41
15a	2	100	80	60:—[d]:40	1.49 (0.34[e])
15b	1	78	58	56: < **1**: 43	1.28
15b	2	100	64	55:—[d]:45	1.22
15c	1	75	54	54:—[d]:46	1.17
15c	2	100	85	53:—[d]:47	1.13
15d	1	71	64	56:—[d]:44	1.27
15d	2	100	64	55:—[d]:45	1.22

[a] All reactions were carried out using the given substrate (10 mmol) in dichloromethane (50 cm^3) at 0 °C. [b] The difference in percentage between the conversion and yield corresponds roughly to the amount of phenolic product. [c] Product compositions were determined by GLC. [d] Not detected. [e] With mixed acid. Taken from ref. 10.

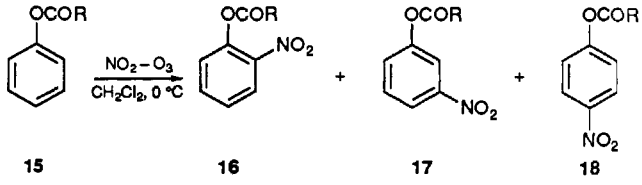
Kyodai-nitration of Phenyl Esters **15**.—Probably because of their sensitivity toward acidic reagents, the literature to date contains little or no report on the successful nitration of aryl esters. To the best of our knowledge, the only available description is that by Modro and Pioch,[10] who treated phenyl acetate **15a** with a stoichiometric amount of nitric acid in ice-cooled sulfuric acid or acetic anhydride and obtained a mixture of *ortho*- and *para*-nitro derivatives **16a** and **18a** in a ratio of *ca.* 1:3.

Compound **15a** underwent nitration rapidly when treated with nitrogen dioxide in dichloromethane in the presence of ozone to give an isomeric mixture of nitro derivatives, in which the *ortho*-isomer **16a** predominated over the *para*-isomer **18a** (*ortho*:*para* = 1.2–1.5). In most cases, the *meta*-isomer **17a** could not be detected. The reaction was accompanied by concurrent deacetylation and the amount of the resulting nitrophenols increased as the reaction proceeded to reach up to 20–30% at complete disappearance of the starting material. The phenolic products were unlikely to arise from hydrolysis of the nitration products but more likely to be derived from the onium intermediate **11** *via* the transfer of acetyl group to some nucleophilic species, *e.g.* nitrate ion (Scheme 4). The resulting phenyl nitrate **13** would rapidly rearrange to 2-nitrophenol **14** through a phenoxy radical–nitrogen dioxide pair as has been verified elsewhere.[11] This was indeed the case; the nitrophenol formed at an early stage was found to be exclusively the 2-nitro derivative **14**.

The other phenyl esters **15b–d** behaved similarly toward the kyodai-nitration, giving a mixture of nitro derivatives in which the *ortho* isomer predominated again (*ortho*:*para* = 1.2–1.3) (Scheme 5, Table 3).

Determination of the isomer distribution of the nitration products requires special caution to minimize inaccuracy arising from partial hydrolysis of the product mixture during the sample manipulation, since the nitrophenyl esters are more readily hydrolysed than their parent compounds. Thus, when an aliquot withdrawn from the reaction mixture was worked up with water before chromatographic determination, the relative importance of the *para*-isomer tended to be overestimated. The low *ortho*:*para* values of 0.34–0.38 claimed by Modro and Pioch[10] may be partly attributed to the aqueous work-up of the reaction mixture.

Because of the similarity between the acylamino and acyloxy groups as polar ring substituents, it is likely that a common mechanism operates in the kyodai-nitrations of the anilides **1** and phenyl acetate **15a**. On the basis of the classical idea, the enhanced *ortho* reactivity may be rationalized by an S_N2 type displacement by the carbonyl oxygen atom on covalent dinitrogen pentaoxide, giving a charged intermediate **8b** which rearranges through a six-membered cyclic transition state to the arenium intermediate **9b** for *ortho*-substitution (Scheme 3). An alternative mechanism to explain the *ortho* enhancement involves the one-electron oxidation of the substrate **15b**. The frontier electron densities calculated by PM3 for the cation radicals **19**, **20** and **21** are shown in Fig. 1.[12] For all the species examined, the unpaired electron densities are highest at the *ortho*/*para* carbon atoms and the heteroatom attached to the ring. Coupling of the cation radical **10b** with nitrogen dioxide at ring carbons leads to the *ortho* and *para* substitution products, while the formation of the *meta* isomer is suppressed because of the unfavourable disposition of the electron-donating acetoxy group in the arenium ion intermediate. The ionic intermediates **11b** and **12b** formed by trapping the radical species **19** with nitrogen dioxide would undergo an intramolecular 1,2- or 1,3-rearrangement of the nitro moiety to give **9b**, a precursor for the *ortho* substitution product. The overall balance leads to enhanced *ortho*-reactivity. The latter mechanistic view is reminiscent of the nitro amine rearrangement intensively studied by White and co-workers,[13] where the heterolytic scission of the protonated nitro amine **22** leads to intermediate **23** composed of two odd-electron fragments (Scheme 6).



a R = Me
b R = Et
c R = Pr^i
d R = Bu^t

Scheme 5

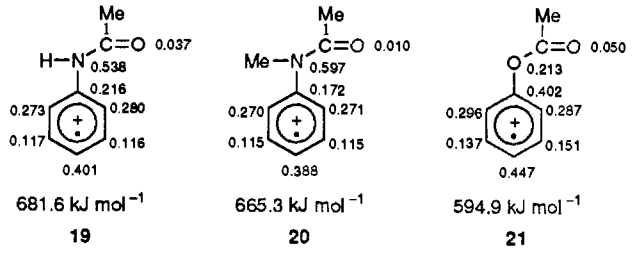
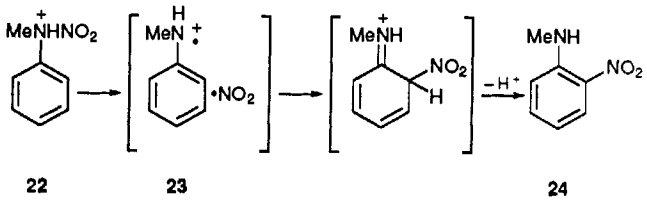


Fig. 1 Frontier electron density and heat of formation for cation radicals derived from compounds **1a**, **4** and **15a** *

* Although the carbon–oxygen double bond is shown to be vertical it is considered to be behind the plane of the paper.



Scheme 6

Recombination of the fragments at a nearby ring position of high unpaired electron density in a solvent cage followed by proton loss leads to the *ortho*-nitro derivative **24**.

The present research has confirmed that anilides and aryl esters behave similarly toward the kyodai-nitration, yielding a mixture of *ortho*- and *para*-nitro derivatives in which the former isomer always predominates. The experimental results together with the calculation of frontier electron densities have added considerable detail to the understanding of the kyodai-nitration process and support our mechanistic view that the cation radicals combine with nitrogen dioxide to form the ionic precursors of the nitration products.

Experimental

General experimental details were given in a previous paper.[1] The anilides **1a–s** and phenyl esters **15a–d** used are all known and prepared from the corresponding acyl chlorides and anilines or phenol. Dichloromethane and chloroform were dried by distillation from calcium hydride. All products except compound **17c** are known and identified by IR, ^{1}H NMR and MS or by direct comparison with authentic specimens.

Molecular orbital calculations were carried out with the MOPAC[12] program (ver. 6.10) using the semi-empirical PM3 method implemented on a Sony Tektronix CAChe system (ver. 3.5). Unrestricted Hartree–Fock wave functions were employed and the calculations were carried out by full optimization using the extra keyword PRECISE.

Kyodai-nitration of Anilides **1**. *Typical Procedure*.—A solution of acetanilide **1a** (10 mmol) in chloroform (50 cm^3) was placed in a three-necked 50 cm^3 flask fitted with two gas inlet tubes and a vent and the mixture was stirred vigorously at 0 °C, while streams of ozonized oxygen and nitrogen dioxide were slowly introduced from separate inlet tubes just over the surface of the liquid mixture. After 2 h the reaction was quenched by the addition of aqueous sodium hydrogen carbonate. The organic phase was separated and worked up as usual to obtain a mixture of isomeric nitroacetanilides **2a** and **3a**.

When both gases were introduced into the solution as fine bubbles, there resulted extensive polynitration. It was necessary to carry out the reaction in the presence of an excess of nitrogen dioxide, otherwise the conversion was low. The reaction time varied depending on the efficiency of the ozone generator employed.

Kyodai-nitrogen of Phenyl Esters **15**. *Typical Procedure*.—A solution of phenyl acetate **15a** (10 mmol) in freshly distilled dichloromethane (50 cm^3) was treated with the nitrogen dioxide–ozone system as described above. The progress of the reaction was monitored by intermittent withdrawal of an aliquot (0.5 cm^3) from the reaction mixture at appropriate intervals. Work-up gave a mixture of nitrophenyl acetates **16a** and **18a** and nitrophenols.

Physical data of the less common nitrophenyl esters are given below:

2-*Nitrophenyl propanoate* **16b**. Oil (lit.,[14] b.p. 102–104 °C/2.5 mmHg); ν_{max}(neat)/cm^{-1} 1773, 1605, 1534, 1352, 1221, 1188 and 1124; δ_H 1.30 (3 H, t, *J* 7.5), 2.69 (2 H, q, *J* 7.5), 7.24 (1 H, dd, *J* 1.3 and 8.1), 7.40 (1 H, dt, *J* 1.3 and 8.0), 7.66 (1 H, dt, *J* 1.3 and 7.9) and 8.10 (1 H, dd, *J* 1.4 and 8.2); *m*/*z* 195 (1.1%, M$^+$), 139 (2), 65 (3) and 57 (100).

3-*Nitrophenyl propanoate* **17b**. M.p. 42–43 °C (lit.,[15] 49 °C); ν_{max}(KBr)/cm^{-1} 1770, 1543, 1473, 1418, 1356, 1217 and 1129; δ_H 1.28 (3 H, t, *J* 7.6), 2.64 (2 H, q, *J* 7.6), 7.45 (1 H, d, *J* 8.2), 7.56 (1 H, t, *J* 8.2), 8.00 (1 H, s) and 8.10 (1 H, d, *J* 8.1); *m*/*z* 195 (0.9%, M$^+$), 139 (1), 123 (1), 109 (1), 93 (3), 76 (1) and 57 (100).

4-*Nitrophenyl propanoate* **18b**. M.p. 63 °C (lit.,[16] 62–63 °C); ν_{max}(KBr)/cm^{-1} 1752, 1622, 1593, 1542, 1534, 1489, 1346, 1206, 1149, 1075 and 1015; δ_H 1.28 (3 H, t, *J* 7.5), 2.64 (2 H, q, *J* 7.6), 7.28 (2 H, d, *J* 9.2) and 8.27 (2 H, d, *J* 9.1); *m*/*z* 195 (0.8%, M$^+$), 139 (1), 123 (2), 109 (2), 93 (2), 76 (1) and 57 (100).

2-*Nitrophenyl* 2-*methylpropanoate* **16c**. Oil (lit.,[17] b.p. 163–164 °C/9 mmHg); ν_{max}(neat)/cm^{-1} 1770, 1605, 1533, 1470, 1352, 1218, 1179 and 1090; δ_H 1.36 (6 H, d, *J* 7.1), 2.89 (1 H, sept, *J* 7.0), 7.22 (1 H, dd, *J* 1.4 and 8.1), 7.38 (1 H, dt, *J* 1.4 and 8.1), 7.64 (1 H, dt, *J* 1.6 and 8.0) and 8.08 (1 H, dd, *J* 1.6 and 8.1); *m*/*z* 209 (1.4%, M$^+$), 139 (32), 109 (8), 93 (3) and 71 (100).

3-*Nitrophenyl* 2-*methylpropanoate* **17c**. Oil; ν_{max}(neat)/cm^{-1} 1763, 1530, 1469, 1352, 1211, 1180 and 1111; δ_H 1.34 (6 H, d, *J* 7.1), 2.85 (1 H, sept, *J* 7.0), 7.44 (1 H, d, *J* 8.1), 7.56 (1 H, t, *J* 8.1), 7.96 (1 H, s) and 8.09 (1 H, d, *J* 8.1); *m*/*z* 209 (0.4%, M$^+$), 139 (13), 123 (1), 109 (1), 93 (8) and 71 (100) (Found: C, 57.3; H, 5.3; N, 6.8. $C_{10}H_{11}NO_4$ requires C, 57.4; H, 5.3; N, 6.7%).

4-*Nitrophenyl* 2-*methylpropanoate* **18c**. M.p. 39–40 °C (lit.,[18] 39–40 °C); ν_{max}(KBr)/cm^{-1} 1761, 1618, 1593, 1534, 1346, 1210 and 1100; δ_H 1.34 (6 H, d, *J* 7.0), 2.85 (1 H, sept, *J* 7.0), 7.27 (2 H, d, *J* 9.3) and 8.28 (2 H, d, *J* 9.4); *m*/*z* 209 (0.4%, M$^+$), 139 (9), 123 (2), 109 (8), 93 (3) and 75 (100).

2-*Nitrophenyl* 2,2-*dimethylpropanoate* **16d**. Oil (lit.,[19] b.p. 90 °C/0.2 mmHg); ν_{max}(neat)/cm^{-1} 2979, 1760, 1607, 1530, 1479, 1352, 1265, 1214 and 1094; δ_H 1.39 (9 H, s), 7.20 (1 H, dd, *J* 1.3 and 8.1), 7.38 (1 H, dt, *J* 1.4 and 8.4), 7.64 (1 H, dt, *J* 1.6 and 8.1) and 8.07 (1 H, dd, *J* 1.6 and 8.1); *m*/*z* 139 (20%), 123 (6), 109 (2), 85 (9) and 57 (100).

3-*Nitrophenyl* 2,2-*dimethylpropanoate* **17d**. M.p. 83–84 °C (lit.,[20] 82–83 °C); ν_{max}(KBr)/cm^{-1} 1751, 1526, 1354, 1275, 1207 and 1113; δ_H 1.38 (9 H, s), 7.42 (1 H, d, *J* 8.1), 7.56 (1 H, t, *J* 8.1), 7.96 (1 H, s) and 8.10 (1 H, d, *J* 8.1); *m*/*z* 224 (0.1%, M$^+$), 139 (3), 93 (2), 85 (15), 76 (2) and 57 (100).

4-*Nitrophenyl* 2,2-*dimethylpropanoate* **18d**. M.p. 97–98 °C (lit.,[16] 94–95 °C); ν_{max}(KBr)/cm^{-1} 1759, 1617, 1592, 1522, 1481, 1348, 1277, 1208 and 1096; δ_H 1.38 (9 H, s), 7.25 (2 H, d, *J* 9.2) and 8.27 (2 H, d, *J* 9.1); *m*/*z* 224 (0.4%, M$^+$), 139 (5), 123 (2), 109 (3), 85 (19), 76 (2) and 57 (100).

Acknowledgements

We acknowledge support of this work by a Grant-in-Aid for Scientific Research No. 05554023 from the Ministry of Education, Science and Culture of Japan.

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Paper 4/06051B
Received 4*th October* 1994
Accepted 18*th October* 1994